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(71) We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with the treatment of mature and immature liver fluke infections and compositions for use in such treatment. The compositions may also contain other active ingredients such as known anthelmintics or fasciolicides.

Sulfonamides in general as well as benzenesulfonamide compounds have been known and synthesized in the art for many years. They have generally been prepared and studied for their activity as anibacterial and diuretic agents and many data have been published concerning the bacteriostatic and diuretic activity of sulfonamide compounds. However, there is no indication that sulfonamides would have acivity against mature and immature liver fluke.

In accordance with the present invention, mature and immature liver fluke are treated in a non-human animal by administering to such an animal a therapeutically effective amount of a compound having the formula:

I

in which R is a hydrogen atom or an amino group; each of X_1 and X_2 is a halogen atom or a trifluoromethyl or nitro group; and each of R_1 and R_2 is a hydrogen atom or a C_{1-3} alkyl group. Examples of C_{1-3} alkyl groups are methyl, ethyl, propyl, butyl, amyl, isoamyl, isopropyl and *tert* - butyl.

When reference is made to "halo" or "halogen" the term includes fluorine, chlorine, bromine and iodine.

The preferred compounds used in accordance with the present invention are represented by formula I where X_1 and X_2 are halogen and in particular when X_1 and X_2 are bromine, e.g. 4 - amino - 3,5 - dibromobenzenesulfonamide, 4 - amino - 3,5 - dibromo - N - methylbenzenesulfonamide, 4 - amino - 3,5 - dichloro - N - ethylbenzenesulfonamide, 3,5 - dibromobenzenesulfonamide, 3,5 - dibromo - N - methylbenzenesulfonamide, 3,5 - dibromo - N - ethylbenzenesulfonamide, and 3,5 - dichloro - N,N - dimethylbenzenesulfonamide.

While many compounds described by formula I are known, some have not been described heretofore. The present invention provides compounds having formula I above in which one or both of X_1 and X_2 are trifluoromethyl groups or in which X_1 is a halogen atom and X_2 is a nitro group, and R, R_1, and R_2 are as defined previously. These novel compounds are exemplified by the following:

3 - nitro - 5 - trifluoromethylbenzenesulfonamide,

3,5 - *bis* - trifluoromethylbenzenesulfonamide,

4 - amino - 3,5 - *bis* - trifluoromethylbenzene sulfonamide,

3 - bromo - 5 - trifluoromethylbenzenesulfonamide,

4 - amino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide,

3,5 - *bis* - trifluoromethyl - N - methylbenzenesulfonamide,

4 - amino - 3 - bromo - 5 - trifluoromethyl - N - isopropylbenzenesulfonamide,

4 - amino - 3 - chloro - 5 - trifluoromethylbenzenesulfonamide,
4 - amino - 3 - bromo - 5 - nitrobenzenesulfonamide,
3 - bromo - 5 - nitrobenzenesulfonamide, and
4 - amino - 3 - chloro - 5 - nitro-N - methylbenzenesulfonamide.

The compounds of the present invention have utility in the field of animal therapy. Tests have shown that such compounds are effective anthelmintics and are especially effective against both mature and immature liver fluke of the species *Fasciola gigantica* and *Fasciola hepatica*, the common liver fluke. in sheep and cattle. The preferred dosage levels depend on the type of compound to be used, the type of animal to be treated, the particular helminth to be combated, and the severity of the helminthic infestation. In general, effective fluke eradication is achieved when the compounds are administered orally at dosage levels of from 1 to 300 mg/kg of animal body weight and preferably from 10 to 100 mg/kg of animal body weight. The compounds used in accordance with the present invention may be administered in a variety of ways depending upon the particular animal, the type of anthelmintic treatment normally given to such animal, the materials and the particular helminths. It is preferred to administer them in anthelmintically effective amounts in a unit oral or parenteral, preferably oral, dose at a time when fluke infection is apparent or suspected in the animal.

In addition to the inactive ingredients, the composition in accordance with the invention may contain one or more other active ingredients which may be selected from the compounds described by formula I or from other known anthelmintic agents. Beneficial results are obtained when the compounds of formula I are combined with an anthelmintic agent such as thiabendazole (2 - (4 - thiazolyl)benzimidazole), tetramisole, (dl - 2,3,5,6 - tetrahydro - 6 - phenylimidazo[2,1 - b]thiazole), Rafoxanide (3,5 - diiodo - 3' - chloro - 4' - (*p* - chlorophenoxy)salicyanilide), Parbendazole (5 - n - butylbenzimidazo - 2 - methylcarbamate, and phenothiazine, known anthelmintic agents.

The amounts of the anthelmintic ingredient in the composition as well as the remaining constituents vary according to the type of treatment, the host animal and the particular helminitic infestation being treated. In general, however, compositions suitable for oral administration, containing a total weight percent of the active compound or compounds ranging from 0.01 to 95% will be suitable with the remainder of the compositions being any suitable carrier or vehicle. A number of modes of treatment may be used and each to some extent determines the general nature of the composition. For example, the anthelmintic compounds may be administered to domesticated animals in a unit oral dosage form such as a tablet, bolus, capsule, or drench; a liquid oil base form suitable for parenteral administration or they may be compounded as a feed premix to be later admixed with the animals feedstuff. When the compositions are to be solid unit dosage forms as in tablets, capsules or boluses, the ingredients other than the active compounds may be any other non-toxic vehicle convenient in the preparation of such forms and preferably materials nutritionally suitable such as starch, lactose, talc, magnesium stearate and vegetable gums. Moreover, when capsules are made, the active compound may be used in essentially undiluted form, the only extraneous material being that of the capsule casing itself which may be hard or soft gelatin or any other acceptable encapsulating material. When the dosage form is to be used for parenteral administration the active material is suitably admixed with an acceptable oil base vehicle preferably of the vegetable oil variety such as peanut oil and cotton seed oil. In all such forms, that is, in tablets, boluses, capsules and oil base formulations, the active compound conveniently ranges from 5 to 80% by weight of the total composition.

When the compounds are used in the form of a drench, the anthelmintic agents may be mixed with or adsorbed on agents which will aid in the subsequent suspending of the active compounds in water such as bentonite, clays, silica, water-soluble starches, cellulose derivatives, gums and surface-active agents to form a dry pre-drench composition, and this pre-drench composition is added to water just before use. In the pre-drench formulation, in addition to the suspending agent, such ingredients as preservatives, anti-foam compounds or other suitable diluents or solvents may be included. Such a dry product may contain as much as 95% by weight of the active compound, the rest being excipient. Preferably, the solid composition contains from 30 to 95% by weight of the active compound. Enough water should be added to the solid product to provide the proper dosage level with a convenient amount of liquid for a single oral dose. From 10 to 30 weight percent of the active ingredient is normally present in orally administered liquid compositions. The commonly used measure in the field is 1 fluid ounce of material and thus 1 fluid ounce of a drench should contain enough of the anthelmintic compound to provide an effective dosage level. Liquid drench formulations containing from 10 to 50% by weight of dry ingredients will in general be suitable with a preferred range being from 15 to 25 weight percent.

When the compositions are intended to be

used in feeds, feed supplements or feed premixes, they will be mixed with suitable ingredients of the animals nutrient ration. Solid orally ingestible carriers normally used for such purposes such as distillers dried grains, corn meal, citrus metal, fermentation residues, ground oyster shells, citrus meal, fermentation residues, attapulgus clay, wheat shorts, molasses solubies, corn cob meal, vegetable substances, toasted dehulled soya flour, soya bean meal feed, antibiotic mycelia, soya grits and crushed limestone are all suitable. The active compounds are intimately dispersed or admixed throughout the active solid carrier by methods such as grinding, melting, or tumbling. By selecting a proper diluent and by altering the ratio of carrier to active ingredient, compositions of any desired concentration may be prepared. Feed supplement formulations containing from 10 to 30% by weight of active ingredient are particularly suitable for addition to feeds. The active compounds is normally dispersed or mixed uniformly in the diluent but in some instances may be adsorbed on the carrier.

These supplements are added to the finished animal feed in an amount adequate to give the final concentration desired for controlling or treating the helminth infection by way of animal ration. Although the preferred level in feeds will depend on the particular compounds, the active compounds of this invention are normally fed at levels of 0.01 to 3% by weight. As stated above, animals are preferably treated at a time when the infestation is apparent or suspected and the preferred method of such treatment is with single oral doses. Thus, administration of medicated feed is not preferred but may be used. Similarly, the amounts of drug present in the feed may be reduced to levels in the order of 0.01% to 0.05% by weight, based on the weight of the feed and the medicated feed administered over prolonged periods. This could be in the nature of a preventive or prophylactic measure. Another method of administering the compounds of this invention to animals whose feeds are conveniently pelleted such as sheep is to incorporate them directly into the pellets. For instance, the anthelmintic compounds are readily incorporated in the nutritionally adequate alfalfa pellets at levels of 2 to 10 g. per pound for therapeutic use and lower levels for prophylactive use, and such pellets fed to the animals.

Examples of compositions suitable for administration to animals are as follows:

Example A

A typical bolus composition is as follows:

4 - Amino - 3,5 - dibromobenzenesulfonamide	6.0 g.
Dicalcium phosphate	1.0 g.
Starch	0.7 g.
Guar gum	0.16 g.
Talc	0.11 g.
Magnesium stearate	0.028 g.

Example B

A typical drench composition is as follows:

3,5 - Dibromobenzenesulfonamide	4.5 g.
Benzalkonium chloride	0.6 ml.
Antifoam emulsion	0.06 g.
Hydroxyethyl cellulose	0.3 g.
Sodium phosphate (monobasic)	0.3 ml.
Water	q.s. to 30 ml.

Examples of typical feed premix supplements are as follows:

Example C

4 - amino - 3,5 - trifluoromethylbenzenesulfonamide	10 lbs.
Corn meal	90 lbs.

Example D

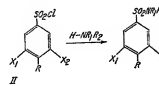
4 - amino - 3 - bromo - 5 - nitrobenzene sulfonamide	20 lbs.
soybean mill feed	80 lbs.

The above feed premix supplements are combined with the animals' regular feed, intimately mixing therewith such that the final concentration of the active ingredient is from 0.01 to 3% by weight.

The fasciolicidal activity of the compounds of this invention is illustrated by the following biological data in which immature liver fluke infestations in sheep were treated with the representative active compounds. The data was obtained by necropsy following the treatment of infected sheep.

Dosage mg/kg)	Live Flukes	Dead Flukes
1. 4 - Amino - 3,5 - dibromobenzenesulfonamide		
100	0	26
100	0	36
100	0	34
2. 3,5 - Dibromobenzenesulfonamide		
100	0	15
100	0	5
100	0	40
50	0	35
50	0	29
50	0	38

The compounds of the invention may be prepared by various processes, some of which are known in the art and which generally culminate with the following reaction:



where R, R_1, R_2, X_1 and X_2 are as previously defined. The benzenesulfonyl chloride (II) is converted to the benzenesulfonamide (I) by treatment with ammonia or a primary or secondary amine to afford the unsubstituted, monosubstituted or disubstituted benzenesulfonamide, respectively.

The reaction of the benzenesulfonyl chloride with ammonia is usually effected with liquid ammonia although aqueous solutions of ammonia have proved successful. A large molar excess of from 5 to 50 times of ammonia is used at temperatures below the reflux temperature of liquid ammonia. The temperature of dry ice is preferred. When aqueous ammonia is used, concentrated solutions are preferred of from 20 to 40% by weight at a temperature of from 0°C. to room temperature. The benzenesulfonamide is isolated by known techniques and procedures.

When the benzenesulfonylchloride is treated with a primary or secondary amine the reaction is preferably effected in a solvent. Inert solvents may be used that will dissolve both the amine and the benzenesulfonylchloride. Solvents must be chosen, however, that will not react with the sulfonyl chloride. Benzene, methylene chloride, chloroform, tetrahydrofuran, toluene and acetone are examples of satisfactory solvents. During the reaction 1 mole of hydrogen chloride is liberated. It is preferred to add to the reaction medium at least 1 mole of a base that will neutralize the liberated HCl but will not react with the benzenesulfonyl chloride. Tertiary amines such as diethylamine and pyridine are satisfactory. Often the tertiary amine can be used in large excess as the solvent. Another method of effecting the same result is to use a large excess of the primary or secondary amine as the solvent. An alternative process comprises the use of an inorganic base such as an alkali metal carbonate or bicarbonate in combination with one of the above listed inert solvents.

In the above reactions which do not employ liquid ammonia, the reaction is run at a temperature of from ambient temperature to the reflux temperature of the reaction mixture. Where liquid ammonia is the reactant the temperature is the temperature of refluxing liquid ammonia.

The reaction is generally carried out for from 1 to 36 hours depending on the temperature, the duration of the reaction decreasing with increase in temperature. In general, the reaction is complete after stirring at room temperature for about 10 hours.

The intermediate benzenesulfonyl chloride compounds may be prepared by several procedures. A benzene compound unsubstituted at the position where the sulfonamide group is desired may be sulfonated using, for example, fuming sulfuric acid to afford the benzene sulfonic acid which may be converted to the benzenesulfonyl chloride with a chlorinating agent such as phosphorus pentachloride. This may also be effected in a single step by treating the above benzene derivative with chlorosulfonic acid.

Aniline derivatives may be used to prepare the desired benzenesulfonylchloride compound by diazotizing the amino group and treating the diazonium salt with cupric chloride and sulfur dioxide. Where the chlorobenzene precursor is available, in which the chloro substituent is activated by a strongly electron withdrawing group such as nitro in the ortho- or para- positions to the chloro substituent, the thiophenol derivative may be prepared therefrom and this converted to the sulfonyl chloride derivative. The thiophenol derivative is thus prepared by treating the chlorobenzene derivative with sodium sulfide, and treating the resultant product with chlorine gas in aqueous acetic acid solution.

In the synthesis of the compounds of formula I it is often necessary to protect certain groups that are susceptable to attack by reagents used in certain of the synthetic steps hereinabove described. The amino group is sensitive to many reagents and may readily be protected by preparing the acetamido derivative or using starting materials that have a nitro group present, and subsequently reducing the nitro compound to the amine. The acetamido derivative is readily prepared from the amine and a carboxylic acid halide or anhydride. The amine can be liberated by acid-catalysed or base-catalysed hydrolysis. The amine can be prepared from the nitro group by catalytic or chemical reduction.

The following examples are typical of the procedure suitable for synthesizing the compounds of this invention. The examples are presented so that the invention might be more fully understood and should not be construed as being limitative of the invention.

EXAMPLE 1

4 - Amino - 3 - bromo - 5 - trifluoromethylbenzenesulfonamide

A. 4 - Nitro - 3 - trifluoromethylbenzenethiol

A stirred solution of sodium sulfide monohydrate, 65.4 g. (0.276 mole), in 1 liter of water is treated with 50 g. (0.222 mole) of 4 - chloro - 2 - trifluoromethylnitrobenzene in 500 ml. of acetone over 1-1/2 hours. The

reaction mixture is stirred for 14-1/2 hours and the resultant solution treated with 25 ml. of concentrated hydrochloric acid. An oil separates from the reaction mixture. This is dissolved in 200 ml. of ether, washed with water and extracted with 2.5 N sodium hydroxide solution. The aqueous solution is washed with ether and acidified with 25 ml. of hydrochloric acid. The resulting oil is extracted with ether and the ethereal solution washed with water affording 47 g. of 4 - nitro - 3 - trifluoromethylbenzenethiol which is used in the next step.

B. 4 - Nitro - 3 - trifluoromethylbenzenesulfonylchloride

A solution of 47 g. of 4 - nitro - 3 - trifluoromethylbenzenethiol in 100 ml. of glacial acetic acid is added dropwise to 1 liter of saturated chlorine water with continuous stirring at from 0—10°C. During the addition the concentration of chlorine is maintained by bubbling more chlorine gas into the solution. Stirring is continued for 1-1/2 hours and the gummy solid precipitate filtered, washed with water and dried at room temperature affording 22.3 g. of a gummy solid. The solid material is taken up in methylene chloride and dried over magnesium sulfate, filtered and evaporated affording an oil which is used without purification in subsequent steps.

C. 4 - Amino - 3 - trifluoromethylbenzenesulfonamide

22.3 g. of 4 - nitro - 3 - trifluoromethylbenzenesulfonylchloride is added dropwise with stirring to 125 ml. of liquid ammonia in a dry-ice bath. The dry-ice bath is removed and the resulting dark solution is stirred the excess of ammonia being allowed to evaporate spontaneously. The residue is treated with water and acetic acid to neutralize the residual ammonia. The solid material thus obtained is washed with water and dried affording 17.8 g. of the crude product. This is recrystallized from toluene using charcoal to afford 10 g. of 4 - nitro - 3 - trifluoromethylbenzenesulfonamide, m.p. 187 to 190°C.

1.0 g. of 4 - nitro - 3 - trifluoromethylbenzenesulfonamide is hydrogenated over 5% Ruthenium on charcoal in 20 ml. of absolute ethanol at room temperature under 40 lbs. of hydrogen for 5 hours. The hydrogen uptake is 100% of theory. The mixture is filtered, evaporated and dried affording 0.87 g. of crude solid. This material is recrystallized from toluene affording 0.75 g. of 4 - amino - 3 - trifluoromethylbenzenesulfonamide, m.p. 150 to 151°C.

D. 4 - Amino - 3 - bromo - 5 - trifluoromethylbenzenesulfonamide

A suspension of 0.69 g (0.029 mole) of 3 - trifluoromethyl - 4 - aminobenzenesulfonamide in 7 ml. of water and 7 ml. of 48% hydrobromic acid is treated dropwise with 0.16 ml. of liquid bromine and stirred for 3 hours at room temperature. The reaction mixture is filtered and the solid material washed with 10% aqueous sodium bicarbonate and water and dried. The dried solid is recrystallized from toluene affording 0.76 g. of 4 - amino - 3 - bromo - 5 - trifluoromethylbenzenesulfonamide, m.p. 248—252°C.

EXAMPLE 2

A. 3,5 - *Bis* - trifluoromethylbenzenesulfonylchloride

A solution of 3,5 - *bis* - trifluoromethylaniline (11.4 g., 0.05 mole), in 40 ml. of glacial acetic acid is treated at room temperature with 8.1 ml. of concentrated hydrochloric acid. The solution is cooled to from −5 to 0°C. and treated with a solution of 3.50 g. (0.051 mole) of sodium nitrite in 7.0 ml. of water over 10 minutes. The resulting suspension is stirred at 0°C. for one hour. This solution is added to a suspension of 50 ml. of glacial acetic acid and 1.0 g. of cupric chloride which is saturated with sulfur dioxide at 0°C. During the addition, gas is evolved from the reaction mixture and when the gas evolution ceases, the reaction mixture is further saturated with sulfur dioxide at room temperature, bubbling the sulfur dioxide into the reaction mixture for approximately 20 minutes. The sulfur dioxide bubbling is stopped and the reaction is stirred at room temperature for 1 hour. The solution is poured onto ice and filtered, and the solid is dried affording 12.45 g. of 3,5 - *bis* - trifluoromethylbenzenesulfonylchloride. It is of sufficient purity to be used as is in the next step.

B. 3,5 - *Bis* - trifluoromethylbenzenesulfonamide

60 to 70 ml. of liquid ammonia in a dry-ice bath is treated portionwise with stirring with 12.4 g. of 3,5 - *bis* - trifluoromethylbenzenesulfonyl chloride. The resulting dark solution is allowed to evaporate spontaneously with stirring. The residue is placed on a water aspirator to remove any excess ammonia and the reaction mixture is treated with a mixture of water and a small amount of glacial acetic acid. The suspension is filtered and the solid material dried affording 10.09 g. of crude product. The crude product is recrystallized from toluene using charcoal, to give 8.73 g. of 3,5 - *bis* - trifluoromethylbenzenesulfonamide, m.p. 183 to 185°C.

EXAMPLE 3

A. 4 - Acetylamino - 3,5 - *bis* - trifluoromethylnitrobenzene

A mixture of 8.2 g. of 4 - nitro - 2,6 - bis - trifluoromethylaniline, 3.6 g. acetic an-

hydride, and 20 ml. of pyridine is heated for 48 hours on a steam bath. The reaction mixture is poured onto ice water and the solid material is filtered, dried and recrystallized from isopropanol affording 4 - acetylamino-3,5 - *bis* - trifluoromethylnitrobenzene.

B. 4 - Acetylamino - 3,5 - *bis* - trifluoromethylaniline

A solution of 7.9 g. of 4 - acetylamino-3,5 - *bis* - trifluoromethylnitrobenzene in 200 ml. of ethanol is hydrogenated under 40 lbs. of hydrogen pressure with 1 g. of 5% palladium on charcoal catalyst. When the calculated amount of hydrogen is consumed, the solution is filtered and concentrated *in vacuo* to give 4 - acetylamino - 3,5 - *bis* - trifluoromethylaniline.

C. 4 - Amino - 3,5 - *bis* - trifluoromethylbenzenesulfonamide

5.7 g. of 4 - acetylamino - 3,5 - *bis*-trifluoromethylaniline is dissolved in 16 ml. of acetic acid and cooled to 10°C., 3.2 ml. of concentrated hydrochloric acid is added, and the mixture cooled to 0—5°C. with stirring. A solution of 1.4 g. of sodium nitrite in 4 ml. of water is added dropwise, with vigorous stirring and the resultant mixture stirred for half an hour. The aqueous diazonium salt solution is then added to a solution of 0.4 g. of cupric chloride in 50 ml. of acetic acid which has been previously saturated at 20°C. with sulfur dioxide. The reaction mixture is stirred for 10 minutes, while sulfur dioxide is bubbled through this mixture and for 20 minutes further. The reaction mixture is poured into ice, extracted with methylene chloride, washed with water, dried and evaporated *in vacuo*. The residual 4 - acetylamino - 3,5 - *bis* - trifluoromethylbenzenesulfonylchloride is again dissolved in methylene chloride and added to an excess of liquid ammonia. The contents of the flask are allowed to evaporate at room temperature overnight, affording 4 - acetylamino - 3,5 - *bis* - trifluoromethylbenzenesulfonamide. This is taken up with 25 ml. of 6N hydrochloric acid and treated on a steam bath for 3 hours. It is cooled in ice and allowed to crystallize. The residue is collected by filtration, washed with water, and crystallized from aqueous ethanol to afford pure 4 - amino - 3,5 - trifluoromethylbenzenesulfonamide.

EXAMPLE 4

4 - Amino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide

A. 4 - Acetylamino - 3 - trifluoromethylbenzenesulfonylchloride

2.0 g. of *meta* - trifluoro - *o* - acetotoluidide and 5.0 ml. of chlorosulfonic acid is heated on a steam bath for 45 minutes. The reaction mixture is poured slowly into a mixture of ice and water. Then, the aqueous suspension is extracted with methylene chloride, washed with water, dried and concentrated *in vacuo* affording 2.0 g. of 4 - acetylamino - 3 - trifluoromethylbenzenesulfonylchloride which is used as is for the next step.

B. 4 - Acetylamino - 3 - nitro - 5 - trifluoromethylbenzenesulfonylchloride

3.0 g. of 4 - acetylamino - 3 - trifluoromethylbenzenesulfonylchloride is dissolved in 15 ml. of concentrated sulfuric acid. 0.9 mole of nitric acid is added dropwise over a period of 15 minutes, while the temperature is kept below 35°C. When the addition is complete the reaction mixture is stirred at room temperature for 2 hours. The reaction mixture is poured onto 150 ml. of ice water and the precipitate is filtered, washed with water and dried affording 4 - acetylamino - 3 - nitro-5 - trifluoromethylbenzenesulfonylchloride, used directly in the next step.

C. 4 - Amino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide

1.3 g. of 4 - acetylamino - 3 - nitro - 5 - trifluoromethylbenzenesulfonylchloride is combined with 13 ml. of concentrated aqueous ammonia and stirred at room temperature for 5 hours. The resultant solution is concentrated to one third of the original volume and the precipitate is allowed to age for 1 hour. The suspension is filtered, washed with water and dried, affording a mixture of 4 - acetylamino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide and 4 - amino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide. The crude mixture (750 mg.) is heated at reflux with 7.5 ml. of 6N hydrochloric acid for 2 hours. The resultant solution is then cooled in an ice bath, and the resulting precipitate filtered, washed with water, recrystallized from aqueous ethanol affording pure 4 - amino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide.

EXAMPLE 5

4 - Amino - 3 - bromo - 5 - nitrobenzenesulfonamide

A. 4 - Acetylamino - 3 - nitrobenzenesulfonylchloride

116.8 g. (0.50 mole) of 4 - acetylaminobenzenesulfonylchloride is dissolved in 600 ml. of concentrated sulfuric acid and cooled to 5°C. A previously prepared mixture of 45 ml. of concentrated nitric acid and 50 ml. of concentrated sulfuric acid is added dropwise at such a rate that the temperature is maintained at from 3 to 6°C. When the addition is complete stirring is continued for 75 minutes at 5°C. The reaction mixture is poured onto 2.5 liters of ice with caution. The supernatant liquid is decanted and the residual material dissolved in hot benzene, separated from some water, cooled and dried over

sodium sulfate. The benzene solution is filtered and the filtrate evaporated to dryness. The residue is triturated with ether and the solid material filtered and used as is in the next step.

B. 4 - Acetylamino - 3 - nitrobenzenesulfonamide

13.1 g. of 4 - acetylamino - 3 - nitrobenzenesulfonylchloride is suspended in 130 ml. of concentrated ammonium hydroxide and stirred at room temperature for 1-1/2 hours. The reaction mixture is concentrated to 1/3 of the original volume by boiling, cooling and filtering. The solid material is recrystallized from 70% ethanol/water affording 7.5 g. of 4 - acetylamino - 3 - nitrobenzenesulfonamide, m.p. 182—183°C.

C. 4 - Amino - 3 - nitrobenzenesulfonamide

7.5 g. of 4 - acetylamino - 3 - nitrobenzenesulfonamide is dissolved in 60 ml. of 6N hydrochloric acid and refluxed for 2 hours. The reaction mixture is cooled, filtered, and the solid material washed with water and dried. The dried 4 - amino - 3 - nitrobenzenesulfonamide has a m.p. of 208—210°C. and is of sufficient purity for use in the next step.

D. 4 - Amino - 3 - bromo - 5 - nitrobenzenesulfonamide

7.0 g. of 4 - amino - 3 - nitrobenzenesulfonamide is suspended in 150 ml. of methanol at room temperature and brominated with 5.2 g. of liquid bromine added dropwise over 15 minutes. The reaction mixture is filtered and the solid material recrystallized from isopropanol affording 4 - amino - 3 - bromo - 5 - nitrobenzenesulfonamide, m.p. 216—218°C.

EXAMPLE 6

3,5 - Dibromo - N - isopropylbenzenesulfonamide

3.0 g. of 3,5 - dibromobenzenesulfonylchloride is added to a solution of 17.7 g. of isopropylamine in 25 ml. of water at room temperature. A complete solution results which is stirred for two hours and poured onto 250 ml. of water. The precipitate is filtered, washed with water, and dried affording 3,5 - dibromo - N - isopropylbenzenesulfonamide, m.p. 105 to 107°C.

EXAMPLE 7

4 - Amino - 3,5 - dibromo - N - isopropylbenzenesulfonamide

4.0 g. of 4 - amino - 3,5 - dibromobenzenesulfonylchloride is added to a solution of 34 ml. of isopropylamine in 30 ml. of water. The resultant solution is stirred overnight at room temperature and poured onto 250 ml. of an ice/water mixture. The precipitate is filtered, washed with water and dried. The dried filtrate is recrystallized from isopropanol affording pure 4 - amino - 3,5 - dibromo - N - isopropylbenzenesulfonamide, m.p. 181 to 183°C.

WHAT WE CLAIM IS:—

1. A method for the treatment of mature and immature liver fluke which comprises administering to a non-human animal susceptible to infestation with mature or immature liver fluke a therapeutically effective amount of a compound having the formula

in which R is a hydrogen atom or an amino group; each of X_1 and X_2 is a halogen atom or a trifluoromethyl or nitro group; and each of R_1 and R_2 is a hydrogen atom or a C_{1-5} alkyl group.

2. A method as claimed in claim 1 in which the compound is orally administered in a daily amount of from 1 to 300 mg/kg of animal body weight.

3. A method as claimed in claim 2 in which the compound is orally administered in a daily amount of from 10 to 100 mg/kg of animal body weight.

4. A method as claimed in any one of claims 1 to 3 in which X_1 and X_2 are both bromine.

5. A method as claimed in claim 4 in which the compound administered is 3,5 - dibromobenzenesulfonamide.

6. A method as claimed in claim 4 in which the compound administered is 4 - amino - 3,5 - dibromobenzenesulfonamide.

7. A method as claimed in any one of claims 1 to 3 in which X_1 and X_2 are both trifluoromethyl.

8. The process that comprises reacting a compound having the formula

where X_1, X_2 and R are as defined in claim 1, with an amine having the formula

$$H—NR_1R_2$$

where R_1 and R_2 are as defined in claim 1,

to produce a compound having the formula set forth in claim 1.

9. A compound having the formula set forth in claim 1, when prepared by a process as claimed in claim 8.

10. A composition useful for treatment of mature or immature liver fluke which comprises a non-toxic carrier or vehicle together with a compound having the formula set forth in claim 1.

11. A composition as claimed in claim 10 containing from 0.01 to 95% by weight of the compound.

12. An orally ingestible solid composition as claimed in claim 11 containing from 30 to 95% by weight of the said compound.

13. A composition as claimed in claim 12, in the form of a tablet, bolus or capsule.

14. A composition as claimed in claim 12, in the form of a pre-drench composition comprising the said compound adsorbed on a suspending agent.

15. An orally ingestible liquid composition as claimed in claim 11 containing from 10 to 30% by weight of the said compound.

16. A composition as claimed in claim 11 in the form of an orally ingestible feed premix containing from 10 to 30% by weight of the said compound.

17. A composition as claimed in claim 11 in the form of an orally ingestible finished feedstuff containing from 0.01 to 3% by weight of the said compound.

18. A composition as claimed in claim 11 in a form suitable for parenteral administration and containing from 5 to 80% by weight of the said compound.

19. A composition as claimed in claim 18 in which the other constituents comprise an oily carrier.

20. A composition as claimed in claim 17 in pelleted form.

21. A compound having the formula

in which X_2, R_1 R_1 and R_2 are as defined in claim 1 and X° is a trifluoromethyl radical

22. A compound as claimed in claim 21 in which R is hydrogen.

23. 3,5 - Bis - trifluoromethylbenzenesulfonamide.

24. 3 - Bromo - 5 - trifluoromethylbenzenesulfonamide.

25. 3 - Nitro - 5 - trifluoromethylbenzenesulfonamide.

26. A compound as claimed in claim 21 in which R is amino.

27. 4 - Amino - 3,5 - *bis* - trifluoromethylbenzenesulfonamide.

28. 4 - Amino - 3 - bromo - 5 - trifluoromethylbenzenesulfonamide.

29. 4 - Amino - 3 - nitro - 5 - trifluoromethylbenzenesulfonamide.

30. A compound having the formula

where R_1 R_1 and R_2 are as defined in claim 1 and hal is a halogen atom.

31. 3 - Bromo - 5 - nitrobenzenesulfonamide.

32. 4 - Amino - 3 - bromo - 5 - nitrobenzenesulfonamide.

33. A process as claimed in Claim 8, substantially as hereinbefore described in any one of Examples 1—7.

34. A compound as claimed in Claim 9, when prepared by a process as claimed in Claim 33.

35. A composition as claimed in any one of Claims 10 to 20 in which the said compound is a compound as claimed in any one of Claims 9, 21 to 32 and 34.

36. A composition as claimed in Claim 10, substantially as hereinbefore described in Example A, B, C or D.

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